REVIEW ARTICLE

New Concepts of Chronic Pain and the Potential Role of Complementary Therapies

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ABSTRACT

Context • The mechanisms of chronic pain involve complex neuroplastic changes at all 3 orders of neurons involved in the transmission of pain as well as changes in the descending inhibitory pathway. Although traditional pharmaceutical therapies have some efficacy, substantial scope exists for a new model of individualized therapy, tailored to the specific response of each patient. Because changes occur at all levels of the pain pathway, successful treatment may require a combination of therapies with different mechanisms of action.

Objective • The research team intended to examine the potential changes within the peripheral nervous system (PNS) and central nervous system (CNS) of patients with chronic pain and to propose a model of chronic pain treatment involving multimodal, complementary therapies for individualized treatment targeting multiple sites along the pain pathway.

Design • The research team performed a review of the literature in the field.

Setting: The study took place in the School of Health and Human Sciences at Southern Cross University (Lismore, New South Wales, Australia).

Interventions • A growing body of evidence supports the use of a variety of complementary therapies to treat chronic pain, including curcumin, capsaicin, vitamin D, omega-3 fatty acids, lipoic acid, acupuncture, yoga, meditation, and mindfulness meditation. These therapies vary with respect to the mechanisms by which they act and the potential areas of effect along the pain pathway.

Results • The literature review showed a number of complementary therapies may be efficacious in reducing chronic pain and/or the need for analgesics, which may offer a reduced adverse effect profile. These therapies include curcumin, capsaicin, vitamin D, omega-3 fatty acids, lipoic acid, acupuncture, yoga, meditation, and mindfulness meditation. Response rates to treatment are likely to vary between people and within therapies.

Conclusions • The available evidence suggests that efficacious complementary therapies exist that target all 3 orders of neurons and, therefore, the authors recommend multimodal individualized treatment for each patient. There is high interindividual variability between patients in responses to treatments. (*Altern Ther Health Med.* [E-pub ahead of print.])

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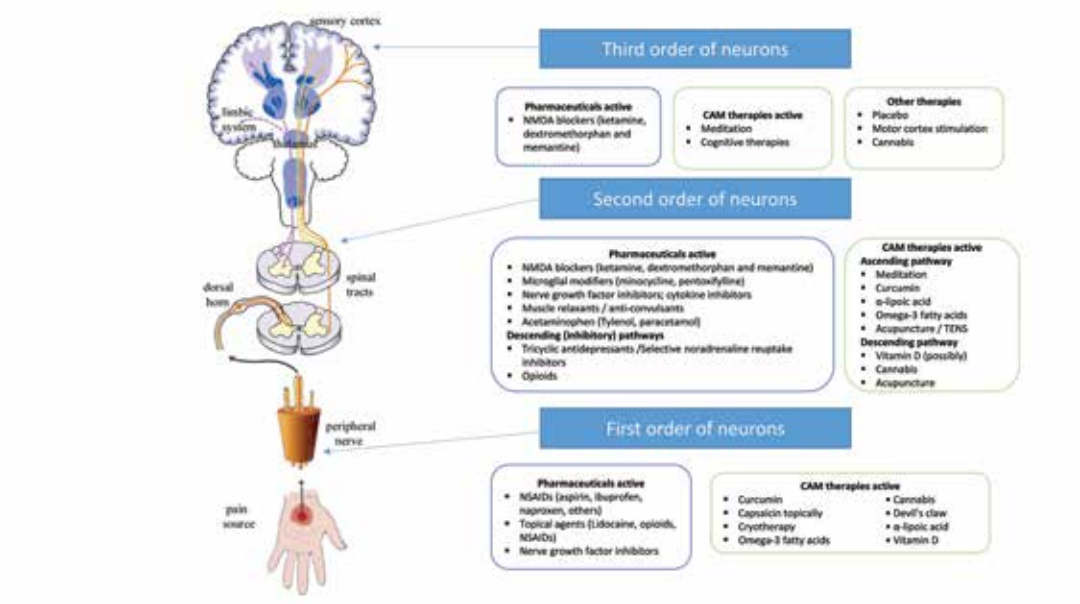
Chronic pain is a major health problem that can affect all facets of life, influencing thinking, mood, and behavior. Between 20% and 31% of people living in Western countries are affected by chronic pain.[1-3] One of the reasons for this high prevalence is that pharmaceutical therapy is only partly efficacious, resulting in approximately a 30% pain reduction for half of chronic pain patients.[4]

Unlike acute pain, which is relatively easily managed, chronic pain presents significant challenges for clinicians. First, many complex, adaptive changes can occur throughout the nervous systems of patients with persistent pain. These changes, termed *neuroplasticity*, can include peripheral and/or central sensitization, which magnifies the pain and/or

Figure 1. Modulation of Pain Within 3 Orders of Neurons



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Abbreviations: CAM, complementary and alternative medicine; TENS, transcutaneous electrical nerve stimulation; NSAIDs, nonsteroidal anti-inflammatory drugs.

the perception of pain.[5] This augmented pain processing can result in diffuse hyperalgesia (ie, increased pain in response to normally painful stimuli) and allodynia (ie, pain in response to normally nonpainful stimuli). Although these changes are often reversible with successful therapy, no consensus exists on the length of time that therapy should continue to achieve optimal outcomes.[4] Furthermore, because changes occur at all levels of the pain pathway, successful treatment may require a combination of therapies with different mechanisms of action.[6]

Another challenge confronting clinicians when addressing chronic pain is that these neuroplastic changes are different in different people and/or etiologies. For instance, patients with neuropathic pain generally have decreased expression of opioid receptors at the dorsal horn, whereas patients with inflammatory pain have increased numbers of opioid receptors.[7] It is therefore no surprise that opioids, which are normally the mainstay of pharmaceutical therapies for severe cancer pain, are ineffective in patients with neuropathic pain.

These recent discoveries have begun to challenge the traditional treatment approaches for managing pain.[8] Rather than an indiscriminative application of analgesics across all patients suffering from chronic pain, practitioners are calling for new strategies using multimodal approaches and including an individualized approach tailored to the individual.[9]

This literature review outlines the most promising complementary therapies for patients with chronic pain and discusses the likely mechanisms of action and potential areas of effect along the pain pathway. In light of recent advances in the understanding of chronic pain, the authors precede the discussions with a review of potential changes within the peripheral nervous system (PNS) and central nervous system (CNS) of patients with chronic pain. Finally, the article concludes with a discussion of how evidence-based complementary therapies might fit into an individualized, multimodal approach to treating chronic pain.

METHODS

A comprehensive literature search was conducted from January to March 2016. Databases searched include Scopus, CINAHL, Medline, Cochrane, and AMED using the following search terms: *neuropathic pain*, *nerve pain*, *chronic pain*, *pain management*, *back pain*, *nonspecific pain*, and *joint pain* in conjunction with terms related to natural or complementary medicine, herbal medicine, or mind-body therapies.

RESULTS

Orders of Neurons

First Order: Peripheral Changes. The first neurons in the pain pathway are the nociceptive, primary afferent neurons, which are close to the skin's surface. Membrane depolarizations normally begin at the peripheral nerve endings, induced by the excitatory effects of hot, cold, mechanical, and chemical stimuli. The action potentials generated at the nerve endings travel up the axon of the peripheral myelinated A fibers and unmyelinated C fibers to the cell body (soma) located in the dorsal root ganglion and continue to the dorsal horn of the spinal cord (Figure 1).[10]

Table 1. Analgesics That Act in the Periphery (First Order of Neurons)

Name of Analgesic	Postulated Mechanism of Action	Adverse Effects
NSAIDs (aspirin, ibuprofen, naproxen, others)	Inhibits the activity of COX-1 and COX-2; decreases prostaglandin synthesis.	Decrease protective prostaglandins, adversely affecting GIT, kidneys, and heart.
Turmeric (curcumin)	Anti-inflammatory activity (reduces prostaglandins, TNF-α, interleukins and nitric oxide); reduces firing of peripheral neurons.	Mild stomach upset, nausea, dizziness or diarrhea; May slow blood clotting.
Capsaicin	Blockade of TRPV1 positive nociceptors; decreases density of epidermal nerve fibers.	High dose capsaicin (8%) can cause burning and pain on application—analgesics required by some patients.
Devil's claw	Possible anti-inflammatory.	Diarrhea.
Cryotherapy (application of ice packs)	Decreases free nerve ending sensitivity.	Generally safe, possible neuropathy or cutaneous nerve injury.
Topical agents lidocaine, cannabinoids, opioids, NSAIDs)	Lidocaine: blocks fast voltage-gated sodium channels in cell membrane of postsynaptic neurons.	Local irritation.
Omega-3 fatty acids	Numerous anti-inflammatory pathways.	Well tolerated.
Vitamin D	Modulates the excitability of neurons.	Hypervitaminosis D results in dehydration, gastrointestinal manifestations and hypercalcemia.
Lipoic acid	In diabetic neuropathy: improves nerve blood flow, antioxidant protection against further neural damage.	Well tolerated in normal doses (oral doses of up to 2400 mg/d resulted in no adverse effects).

Abbreviations: NSAIDS, nonsteroidal anti-inflammatory drugs; COX-1, cyclooxygenase 1; COX-2, cyclooxygenase 2; TNF-α, tumor necrosis factor alpha; TRPV1, transient receptor potential vanilloid 1; GIT, gastrointestinal tract.

Peripheral nerve endings contain 3 different types of receptors/ion channels, which are sensitive to a number of substances released in the inflammatory cascade that cause pain. These substances include bradykinin, prostaglandins, substance P, leukotrienes, cytokines, nitric oxide (NO), and growth factors. If the insult causing the pain persists, these mediators can contribute to long-term sensitization of the nociceptors, through ectopic discharges and lowered firing thresholds.[10]

If nerves are damaged, changes in the expression of receptors/ion channels can occur at the point of damage. An increased sensitivity to touch and pressure can also be present due to increased reactivity of the mechanoreceptors, resulting in spontaneous pain.[10] Collateral sprouting, which consists of a growth of intact nerve fibers into the damaged nerve area, may also occur, thus expanding the peripheral receptive fields.[11]

This combination of changes in the peripheral nerve endings causes changes in the cell bodies within the dorsal root ganglion that promote cross-excitation of other cell bodies. The increased sensitivity of the peripheral nerves prime the spinal impulses to exhibit enhanced, evoked responses to stimuli.[5]

A number of pharmaceutical agents may be effective in reducing peripheral transmission of pain. These include local anesthesia, which blocks the fast voltage-gated sodium channels in the neuronal cell membrane. Other agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs), cytokine inhibitors, and growth factor inhibitors, target the various components of the inflammatory cascade. Although not analgesics in their own right, glucocorticoids injected into the site of injury or applied topically to injuries involving the inflammatory cascade can reduce most aspects of the inflammation. Table 1 lists the most successful agents for addressing the pain signals prior to their entry into the CNS, their general mechanisms of action, and important contraindications and adverse effects.

Second Order: Spinal Sensitization. The first order of neurons terminates in the dorsal horn of the spinal cord and synapse with second-order neurons (ie, A and C fibers) that travel through the spinothalamic tract. The majority of primary afferent nerves use glutamate at the synaptic terminal. Glutamate exhibits its excitatory effect on a number of receptors, including the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and the *N*-methyl-D-aspartate (NMDA) receptors. At both of these receptors, binding of the glutamate to the receptor opens ion channels, allowing free calcium (Ca^{2+}) to rush into the cell. As it enters the cell, depolarization occurs, initiating an action potential that is sent up the spinal cord.

When glutamate is released from sensory afferent neurons in response to acute or low-frequency pain, it is the AMPA receptor that is involved. The AMPA receptors can be increased in number due to chronic pain; however, they have a regulatable switch that controls glutamate-evoked entry of Ca^{2+} into neurons.[11] Conversely, the NMDA receptors have no such mechanism and are often thought to be the key mediators of pathological pain.[11]

The NMDA receptor becomes involved if a repetitive or high-frequency stimulation of the C fibers occurs.[5] Repetitive excitation of NMDA receptors results in a progressive increase in the frequency and magnitude of firing of dorsal horn neurons, known as windup.[12] In nerve injury, these changes are accompanied by a downregulation of spinal glutamate transporters, resulting in disruptions of glutamate

Table 2. Analgesics That Act in the Spinal Cord (Second Order of Neurons)

Name of Analgesic	Mechanism of Action	Adverse Effects
NMDA blockers (ketamine, dextromethorphan, and memantine)	Deactivate the NMDA receptor by either competing with the binding of glutamate or glycine or by binding to allosteric sites or blocking ion channels by binding to a site within them.	Narrow therapeutic window, psychiatric symptoms, addictive.
Microglia modulation (minocycline, pentoxifylline, and propentofylline)	Anti-inflammatory effects on microglial cells and neurons.	Headache, dizziness, gastrointestinal disturbances.
Curcumin	Inhibition of TNF-α in spinal cord.	Mild gastrointestinal symptoms; may slow blood clotting.
Nerve growth factor inhibitors and cytokine inhibitors	Decrease pain sensitivity by decreasing intraepidermal nerve fiber density.	Increase in symptoms of osteoarthritis.
Muscle relaxants	Potentiation of $GABA_A$ receptor-mediated synaptic inhibition.	Sedation, drowsiness and dependence.
Paracetamol (acetaminophen)	Inhibits the activity of COX-3 mainly in the CNS.	Liver toxicity.

Abbreviations: TNF-α, tumor necrosis factor alpha; COX-3, cyclooxygenase 3; CNS, central nervous system.

homeostasis and excess glutamate. These changes ultimately result in a bilateral increase in the magnitude of response to painful stimuli, even if the original insult was unilateral.[13] From a clinical perspective, this outcome means that chronic pain results in a bilateral amplification of pain, even if it originated unilaterally.

Two types of glial cells (ie, the nonneuronal support cells in the CNS) are the microglia and the astrocytes, and they are involved in the modulation of neurotransmission. Microglia are similar in origin and function to the macrophage. Their role in chronic pain appears to include the secretion of proinflammatory cytokines, which play an important role in sensitization of the CNS and may contribute to allodynia and hyperalgesia.[14]

Astrocytes are phagocytic cells that regulate the extracellular ion concentration of potassium (K^+) and Ca^{2+} and help degrade the excess neurotransmitters that spill out of the synaptic cleft, particularly glutamate. In chronic pain, however, astrocytes contribute to central sensitization and can actually release glutamate.[5] In general, activation of the microglia and astrocytes leads to those cells releasing substances that enhance neuronal activity, potentially leading to a positive feedback loop of increased microglial involvement and more pain.

Many pharmacological interventions are aimed at decreasing transmission of impulses through the second order of neurons in the spinal cord and/or addressing the neural plasticity found there. NMDA blockage includes ketamine, a potent channel blocker, and the weaker agents, dextromethorphan and memantine. The narrow therapeutic window of these drugs prevents the majority of patients from achieving complete resolution of their pain.[16]

Other interventions include cytokine inhibitors and drugs that modulate microglia, such as minocycline, pentoxifylline, and propentofylline. Although the theoretical and experimental evidence supporting these drugs is good, the controlled clinical trials have been largely disappointing.[10] The γ-aminobutyric-acid (GABA)-ergic drugs pregabalin and gabapentin, which are anticonvulsants used to treat chronic pain in conditions such as diabetic neuropathy and postherpetic shingles, as well as opioids and antidepressants, can reduce the transmission of impulses by binding at presynaptic and postsynaptic receptors in the first and second order of neurons, respectively. Their actions are discussed further under the discussion of the modulation of pain. Table 2 lists the most successful agents that act at the second order of neurons, their general mechanisms of action, and important contraindications and adverse effects.

Third Order: Supraspinal Mechanisms. After the nociceptive stimulus travels through the A and C fibers of the spinal cord, it goes to a number of specific areas in the brain, including (1) the primary and secondary somatosensory cortices, which localize and interpret the stimuli; (2) the anterior cingulate cortex, which is involved in anxiety and anticipation of pain; and (3) the limbic system, which is involved in the emotional aspects of pain, including fear. Other areas that receive the impulses include the nucleus accumbens, which is involved in placebo analgesic effect, and the insular cortex, which may contribute to negative emotional responses.

Newer imaging techniques have found that the brains of patients with chronic pain differ from those of normal patients in metabolism and regional concentrations of neurotransmitters. Changes in both grey and white matter also occur in many of the specific areas identified above. For example, repeated painful stimulation results in a substantial increase in grey matter in somatosensory areas.[16,17] In addition, if the chronic pain is due to neuropathic pain, cortical reorganization occurs after injury, and the extent of the changes seem to correlate with the degree of pain.

Little evidence exists that the maladaptive neuroplastic changes that occur in the brain as a result of chronic pain can be directly reversed by any pharmaceutical therapy, with the exception of NMDA receptor antagonists.[10] Direct motor cortex stimulation, repetitive transcranial magnetic stimulation, transcranial direct current stimulation, and deep brain stimulation have shown some efficacy.[10] Other nonpharmaceutical treatments that have proven effective

Table 3. Therapies That Act at Supraspinal Levels to Decrease Pain or Perception of Pain

Name of Analgesic	Mechanism of Action	Adverse Effects
Meditation	Reduces lateral and prefrontal cortex activity; positive effect on mental health.	
Cognitive therapies	Reduce activity in the brain regions involved in affective and cognitive modulation of pain; positive effect on mental health.	
Placebo	Release of endogenous opioids; positive effect on expectations.	
Opioids	Activate the descending inhibitory pathway.	Rebound hyperalgesia, substance abuse.
NMDA blockers (ketamine, dextromethorphan, and memantine)	Short lived improvements in mood; slows CNS function.	Feelings of intoxication, psychiatric symptoms, addictive.

Abbreviation: CNS, central nervous system.

Table 4. Analgesics That Act on the Descending Inhibitory Pathway (the Endogenous Analgesic System)

Name of Analgesic	Mechanism of Action	Adverse Effects
Opioids	Opioids are agonists of the μ-opioid receptors, decreasing transmission of pain from the first order of neurons to the second order of neurons.	High rate of multiple adverse effects including itch, nausea, vomiting, constipation, drowsiness, dry mouth, dependence, and respiratory depression.
Cannabis/cannabinoids	Cannabinoids are agonists at the cannabinoid receptors, decreasing transmission of pain from the first order of neurons to the second order of neurons.	Headache, nausea, nasopharyngitis, somnolence, dizziness, and rebound hyperalgesia.
SNRIs	Increase time of noradrenaline presence in synaptic cleft, thereby reinforcing the descending inhibitory pathway.	Loss of appetite, weight loss, sleep disturbances, and increase in suicidal thoughts.
TCAs	Increase time of 5-HTP presence in synaptic cleft, thereby reinforcing the descending inhibitory pathway.	Sedation, postural hypotension, blurred vision, dry mouth, and constipation.
Omega-3 fatty acids	Enhance concentrations of endocannabinoids.	Well tolerated.
Acupuncture	Activates a variety of bioactive chemicals in the inhibitory pathway including opioids, serotonin and noradrenaline.	Not associated with serious harmful events if properly performed.

Abbreviations: SNRIs, selective serotonin–norepinephrine reuptake; TCAs, tricyclic antidepressants; 5-HTP, 5-hydroxytryptophan.

within the brain are discussed later in this review. Long-term resolution of chronic pain with therapies aimed at other areas in the pain pathway may also indirectly lead to a reversal of the maladaptive changes in the brain.[10,18] Table 3 lists the most successful therapies that act at the supraspinal level of neurons, their general mechanisms of action, and important contraindications and adverse effects.

Modulation of Pain

The human body evolved its own endogenous analgesic system to help decrease pain when feelings of intense pain were likely to reduce the chances of survival or when extreme pain reached levels that adversely affected other bodily functions. Today, this analgesic network explains why athletes may not feel the full extent of an injury until the end of a game and why patients who rush to emergency wards with their injuries often report rapidly increasing pain after their arrival. Decreases in this inhibitory control are possible in nerve injury and chronic pain conditions, provoking tactile allodynia and hyperalgesia.[5]

These inhibitory signals originate in the amygdala and hypothalamus and result in the release of 5-hydroxytryptophan (5-HTP) and dopamine into the synaptic cleft of the interneuron. This action, in turn, causes the release of endogenous opioids and cannabinoids into the area near the synaptic gap between the first and second order of neurons.[19] The release of these substances results in both presynaptic and postsynaptic inhibition of the propagation of impulses. GABA-releasing interneurons are also involved in reducing transmission of impulses in this system.

Several pharmaceuticals are aimed at these modulation pathways. Opioids are potent modulators of pain; however, long-term use of opioids results in downregulation of the number of opioid receptors and can cause opioid-induced hyperalgesia.[20] Serotonin and norepinephrine reuptake inhibitors and tricyclic antidepressants increase the time that the noradrenaline and 5-HTP remain in the synaptic cleft. These drugs have been found to be efficacious in treating both chronic pain and some of the psychological manifestations of that pain. Pregabalin and gabapentin are GABA-ergic drugs that inhibit the release of excitatory neurotransmitters, such as glutamate and substance P, and inhibitory transmitters, such as noradrenaline and serotonin.[21] Table 4 lists the most successful therapies that modulate painful stimuli in the CNS and the major adverse effects of those therapies.

Complementary Therapies

As detailed previously, chronic pain results in complex, adaptive changes in all 3 orders of neurons, and these changes ultimately increase the transmission and/or perception of pain. As different individuals experience different changes and combinations of changes, the paradigm for chronic pain management needs to shift toward a more individualized, patient-centered approach. Complementary therapies have the potential to be used in that way, to suit an individual patient's needs with fewer adverse effects than pharmaceutical agents. The following text discusses the uses and mechanisms of action of a range of evidence-based natural therapies that are designed to address the biological, psychological, and spiritual aspects of chronic pain.

Omega-3 Fatty Acids. Omega-3 fatty acids are a family of fatty acids that have triple double bonds. α-Linolenic acid is widely found in plant food, whereas the 2 major omega-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid, are found preformed, particularly in marine sources.

One of the key benefits attributed to the omega-3 fatty acids is their ability to decrease inflammation, via their action on the cyclooxygenase (COX) and lipoxygenase (LOX) enzymes. Although targeting the same enzyme pathways as some pharmaceutical agents (eg, NSAIDS), omega-3 fatty acids have a much slower mechanism of action. A change in the membrane's fatty acid composition is required, which may take weeks and can be affected by other dietary factors, particularly the intake of alternate fatty acids, such as the more proinflammatory omega-6 fatty acids.

Omega-3 fatty acids also affect the production of various anti-inflammatory compounds called *resolvins*, *protectins*, and *maresins*.[22] These compounds may suppress somatic inflammatory pain, at least in part by modulating the activities of transient receptor potential (TRP) channels, particularly TRP vanilloid 1 (TRPV1) and TRP ankyrin 1 (TRPA1).[23] Although TRP channels have an important role in a number of normal physiological processes, such as signal transmission, TRP channel dysfunction is believed to be involved in a number of disease states, including chronic pain. Omega-3 fatty acids may therefore play a key role in reducing chronic pain.

The omega-3 fatty acids have been shown to be useful for reducing pain in osteoarthritis (OA),[24] rheumatoid arthritis,[25] and other pain syndromes, such as inflammatory bowel disease and dysmenorrhea.[26] In rheumatoid arthritis, intervention with omega-3 fatty acids can result in a decrease in NSAID and paracetamol use.[27,28] Supplementation with omega-3 fatty acids, given as a treatment for chronic nonspecific neck and back pain, has also shown large numbers of patients discontinuing NSAID medications for pain control.[29] From a clinical perspective, omega-3 fatty acids are often used as an adjunct prescription with other natural anti-inflammatories or pharmaceutical pain medications.

While the predominant actions of omega-3 fatty acids are attributable to their anti-inflammatory compounds, these fatty acids use other subtler means to affect pain. Chronic pain and depression often coexist, and the relationship can be bidirectional in nature and can share a common biochemical instigator, the cytokine tumor necrosis factor alpha (TNF-α).[30] Supplementation with omega-3 fatty acids may reduce TNF-α levels[31] and may be used in the treatment and prevention of depressive diseases.[32] Therefore, one could speculate that part of the omega-3 fatty acids' effects in chronic pain may be via the effect on depressive symptoms.

Aside from their peripheral actions in decreasing inflammation, omega-3 fatty acids are also thought to work centrally. A 12-week dietary intervention in patients with chronic headaches demonstrated that manipulating the endocannabinoids derived from omega-3 and omega-6 fatty acids in humans could affect clinical outcomes, including reduction in pain, psychological distress, and use of medication for acute pain.[33]

The authors mentioned previously how long-term use of opioids can result in downregulation of the number of opioid receptors and opioid-induced hyperalgesia. An animal study has shown the potential of omega-3 fatty acids as an adjuvant treatment to acute morphine treatment, with an increase in the antinociceptive action of morphine and the attenuation of morphine tolerance with chronic morphine administration.[34]

The available research suggests that omega-3 fatty acids may have multiple beneficial actions, acting across all 3 orders of neurons. They may be beneficial as an adjunct or stand-alone treatment for a range of chronic pain disorders, particularly arthritic or musculoskeletal pain, and may decrease reliance on or even potentiate the effects of opioid or NSAID medications.

Turmeric. The rhizome of the turmeric plant (*Curcuma longa*) has been used for centuries for culinary and medicinal purposes. It contains approximately 5% phenolic curcuminoids, of which curcumin is the primary component. Curcumin is one of the most extensively studied plant compounds in modern phytotherapy, demonstrated to influence a wide variety of molecular targets, including transcription factors, cytokines, growth factors, and several enzyme pathways, with resulting anti-inflammatory activity being a major outcome.[35]

A large number of trials have examined the anti-inflammatory effects of curcumin, demonstrating pharmacological actions on nuclear factor kappa B (NF-κB) that account for much of its downstream anti-inflammatory activity, including reduction of prostaglandins, TNF-α, interleukins, and NO.[36,37]

OA pain, a largely inflammatory condition, has been a strong area of research interest. Different curcumin preparations have shown significant reductions in pain, often occurring in conjunction with reductions in NSAID consumption.[38-40] Significant pain reductions have also been seen in conditions of postoperative inflammation[41] as have beneficial effects in pain-related decreases affecting quality of life for patients with solid tumors.[42]

A recent meta-analysis on the analgesic effect of curcuminoids found a significant effect for bioavailable curcuminoid supplementation in reducing pain severity

(SMD, -0.98; 95% confidence interval [CI], -1.81 to -0.15; $P = .02$). In addition, the studies that used a visual analogue scale (VAS) for assessment of pain severity found a reduction of -19.33 points (95% CI, -29.80 to -8.87; $P = .0003$).[37]

Supplementation of NSAIDs with curcumin has not shown significant benefits[43,44]; however, noninferiority trials have found similar effects on pain for curcumin preparations and ibuprofen[45] and also compared to acetaminophen. However, one study found curcumin to be inferior to the NSAID nimesulide.[46]

The mechanism of action of curcumin for pain relief has been investigated through a series of animal pain models, particularly in neuropathic pain. Many of the mechanistic studies have used intraperitoneal or intrathecal administration to elucidate pain pathways affected by curcumin, showing marked activity in the spinal cord and dorsal root ganglions through inhibition of glial activation and reduced production of inflammatory mediators in the spinal cord.[47-52]

Curcumin absorption has presented a persistent problem, with the pharmacokinetic profile showing low uptake and limited distribution of curcuminoids throughout the tissues, with a peak serum concentration demonstrated 1 to 2 hours after an oral dose.[53] Many methods of improving bioavailability have been explored, with the proprietary formulations Meriva and Theracurmin showing significantly improved oral bioavailability over turmeric.[46,54]

Due to the bioavailability issues outlined, oral administration is not likely to achieve the same significant levels of curcuminoids as when administered intravenously or intrathecally as in animal studies. However, many animal trials also have demonstrated significant antinociceptive effects with orally administered curcumin. For example, diabetic neuropathy models in rats and mice have shown dose-dependent antinociceptive effects, with increased tolerance to heat and pressure,[55-57] which occurred in conjunction with the inhibition of TNF-α in the spinal cord in one study.[50] Other neuropathic pain models have found oral administration to attenuate hyperalgesia and mechanical allodynia.[52,58] Effects were seen in the peripheral level of neurons within the adenosine triphosphate-sensitive potassium channels, occurring in conjunction with decreased pain behaviors.[59]

These studies suggest that nociceptive activity may occur across different mechanisms within both the spinal cord and peripheral neurons. In addition, turmeric also has an excellent and well-established safety profile, with extracts containing up to 8 g of curcuminoids being well tolerated in human studies with daily administration for up to 6 months.[60] Given the mechanisms of action outlined above, turmeric is most likely to provide the greatest benefit for patients with inflammatory pain.

Capsaicin. Capsaicin is a capsaicinoid isolated from *Capsicum* species and is the principal spicy component of chillies. Used topically, capsaicin has been well researched for the treatment of neuropathic pain in a variety of conditions, including postherpetic neuralgia, neuropathy in connection with human immunodeficiency virus (HIV), diabetic peripheral neuropathies, and also OA.

Capsaicin has a unique mechanism of action; its effects take place within the TRP family of ion channels, particularly TRPV1, located within the C fibers of the peripheral neurons. Pain fibers expressing TRPV1 are located throughout the CNS in areas that process pain signals and also appear to be upregulated in the setting of neuropathic pain.[61] Activation of the channel can cause a sensation of burning pain, and an effective blockade of TRPV1-positive nociceptors has been demonstrated through topical application of capsaicin.

Mechanistic research suggests that repeated treatment with capsaicin may reversibly decrease the density of epidermal nerve fibers, reducing the transmission of pain sensation after treatment for several weeks or months.[62] Capsaicin application in humans has demonstrated significantly reduced pain ratings upon exposure to high-frequency stimulation (47%), has reduced hyperalgesia potentiation by 92%, and has been shown to decrease the area of secondary hyperalgesia by 76%.[63] The initial use of low-dose, repeated-application creams has been largely replaced with the introduction of high-dose patches.

The high-dose (8%) capsaicin patch has been licensed in Europe since 2009 for the treatment of peripheral neuropathic pain in nondiabetic adults and has been shown to provide pain relief in some people for up to 5 months with a single application.[64,65] It is effective for conditions with little to no inflammatory pain, including postherpetic neuralgia, HIV-associated neuropathy, and cancer-related neuropathic pain. A Cochrane review including studies totaling 2073 participants found benefits in using the 8% patch over a lower concentration (0.04%) of capsaicin for postherpetic neuralgia and HIV neuropathy.[66]

Other studies have found capsaicin to be less effective. In a meta-analysis of individuals with postherpetic neuralgia (N = 1248), 22% of those treated with high-dose (8%) and 39% treated with low-dose (0.04%) capsaicin had no response to treatment; in addition, 1.5% of patients in the high-dose group and 0.8% in the low-dose group had worse pain during treatment.[67]

For those who do respond to treatment with capsaicin, a significant benefit in the use of the high-dose patch is that it requires only a single application, whereas the lower-dose creams require repeated application and may not develop adequate desensitization.[61] The high-dose application can, however, be associated with an intense burning sensation, thus requiring a topical anesthetic, such as lidocaine. Sometimes an oral or intravenous anesthesia is used[68]; however, some researchers have found that using an anesthetic may not be necessary. In a retrospective analysis of anesthetic versus no anesthetic in patients with neuropathic pain who were treated with an 8% capsaicin patch (n = 58), no significant benefits were found for pain scores or treatment effects with the use of lidocaine,[69] and experienced clinicians suggest that only a minority of patients require pharmaceutical analgesia.[65]

Cannabis. At this time, it is impossible to place marijuana universally into pharmacological or complementary category due to the varying laws regulating its use. Marijuana has been used medicinally for centuries for pain reduction, and cannabinoid receptors have been found in all 3 orders of neurons. Tetrahydrocannabinol and other cannabinoids reduce the NMDA receptor by 30% to 40% and have been found to have other beneficial effects in chronic pain. The modulation of central GABA and glutamate by cannabinoids occurs in various locations throughout the brain, including the cortex, the amygdala, and the hippocampus.[70]

Clinically, the effect on pain reduction is modest, with differing therapeutic delivery options and different cannabinoid profiles—synthetic molecules vs complex botanicals—possibly having a bearing on the clinical effect.[71] A meta-analysis on the use of cannabinoids found that the reduction in chronic pain achieved averaged 37%, compared to a placebo at 31%, with other benefits including decreased spasticity, especially in multiple sclerosis, and decreased nausea and vomiting for chemotherapy patients—47% versus 20% for placebo.[72] A study assessing the long-term safety of cannabis use for chronic noncancer pain treated 215 individuals with a median dose of 2.5 g/d, and compared the results for 1 year to those of 216 control participants, who had chronic pain but did not use cannabis. They found no difference in the risks of serious adverse events but an increased risk in nonserious adverse events (adjusted IRR, 1.73), including headache, nausea, nasopharyngitis, somnolence, and dizziness.[73]

Devil's Claw. The secondary tuber of devil's claw (*Harpagophytum procumbens*) contains a range of iridoid glycosides, including harpagoside, which is widely regarded as the active constituent.[74,75] Devil's claw is commonly used for musculoskeletal pain disorders such as OA and back pain, and a wide range of placebo-controlled trials, particularly in OA, have shown evidence of significant analgesic effect.[74,76-81] A Cochrane review of herbal medicine for low-back pain found that 50 or 100 mg daily of an extract of devil's claw standardized to harpogoside (2 trials, n = 315) was more effective than placebo for treating low-back pain, whereas one trial suggested equivalence to 12.5 mg of the NSAID rofecoxib.[82] That study also noted methodological flaws in several studies that decreased the reliability of the data.

One pharmacological study in humans tested for changes in LOX and COX inhibition before and after 2 g of powdered devil's claw was given to healthy individuals for 21 days.[83] The researchers found no significant differences between baseline and postintervention and concluded that the supplement was not in the same class as NSAIDs. A separate in vivo study showed an inhibitory effect on proinflammatory cysteinyl leukotrienes, with inhibition of up to 58%.[84]

Experimental models have not been consistent in demonstrating positive anti-inflammatory or antinociceptive activity.[75,80] The only available research at the current time to suggest a mechanism of action for devil's claw comes from animal and in vitro studies. These studies have suggested an antinociceptive effect as a result of an opioidergic mechanism,[85] inhibition of COX-1 and COX-2 expression, and inhibition of TNF-α and NO[86] as well as a protective effect for cartilage that is particularly related to its use in OA.[87-89] This protective effect is supported by in vitro testing of isolated fractions of devil's claw, showing inhibition of COX-1, COX-2, NO, NF-κB, TNF- α, and leukotriene.[84,86,88,90,91]

Overall, the in vitro data suggest a range of potential mechanisms to reduce inflammation and protect cartilage from destruction, although clinical effectiveness is mixed. More robust research into this herb is needed.

Caffeine as Adjuvant Analgesic. Caffeine has been investigated for an additive analgesic effect when used in conjunction with common analgesics such as paracetamol, ibuprofen, and aspirin. A Cochrane review found that the doses of caffeine most commonly evaluated for effectiveness were those from 100 mg to 130 mg, with the treatments being used in conditions such as postpartum pain, postoperative dental pain, and headache (N = 4262). The review found a small but statistically significant benefit, with approximately 5% to 10% more participants achieving a good level (50% or more) of pain relief. The number needed to treat for benefit was 14.[92]

Caffeine is not believed to have an intrinsic antinociceptive effect; however, through a range of proposed mechanisms, including pharmacodynamic and pharmacokinetic aspects, it appears able to potentiate the action of analgesics.[93] The effects appear to be mediated largely through the A_{2A} and A_{2B}-adenosine receptors, the antagonism of which has antinociceptive effects.[94] It is thought that the addition of caffeine to analgesia is generally safe, and it has been a common addition to medications for that potentiation.[92,95]

Vitamin D. Vitamin D is produced endogenously within the body after exposure to sunlight and can also be obtained through foods. Some of the best sources of vitamin D include oily fish, cod liver oil, egg yolk, and liver. The main forms of vitamin D are cholecalciferol—vitamin D_3—and ergocalciferol—vitamin D_2, and although classified as a fat-soluble vitamin, the main active form of vitamin D (1,25-hydroxyl vitamin D) actually functions as a neuroactive steroid hormone.[96,97] Deficiency or insufficiency of vitamin D appears to be widespread and inadequate vitamin D levels can occur readily even in countries with high levels of sunlight exposure, such as Australia, where it affects nearly one-third of adults older than 25 years.[98]

Vitamin D plays an essential role in bone metabolism and muscle function,[97] and vitamin D deficiency appears to be strongly correlated with nonspecific musculoskeletal pain,[99-101] which is often misdiagnosed.[102]

Supplementation with vitamin D has been well studied for chronic musculoskeletal pain states, with varying levels of success. A Cochrane review into vitamin D and chronic pain concluded that "a large beneficial effect for vitamin D across different chronic painful conditions is unlikely." However, the reviewers reported issues with a number of the included studies, citing methodological concerns such as identification of deficiency states and the reporting of responders and nonresponders.[103]

Certainly, the response to vitamin D supplementation on pain has been mixed, and that result could partly be due to the degree of vitamin D deficiency in individual studies, the diagnosis of vitamin D deficiency, the supplemental dose given, and the variability of the conditions measured.[97,104] For example, in a study of Australian older men, chronic pain was not associated with blood 25-hydroxy vitamin D status, the main measure used for assessing such status, but with 1,25-hydroxy vitamin D, a vitamin D metabolite formed from the renal conversion of 25 hydroxy vitamin D.[104]

A recent trial (N = 80), not included in the Cochrane review, showed a reduction in VAS scores for pain and in the inflammatory biomarkers TNF-α and prostaglandin E_2 by 24 points, 54%, and 39%, respectively, with the use of 4000 IU of vitamin D daily in conjunction with the patients' usual analgesic regimens, for 3 months.[105] The reductions were statistically significant only with time within the vitamin D group but were not significantly different between groups, likely due to an underpowered study.

Although the clinical efficacy of vitamin D supplementation in chronic pain is yet to be fully elucidated, a number of possible mechanisms have been suggested by which vitamin D could be involved in pain, and these mechanisms include all 3 orders of neurons. In the first order, vitamin D is able to modulate the excitability of neurons and may lower the firing threshold of sensory neurons by degrading prostaglandins and inhibiting COX-2 expression. In the second order of neurons, the transmission of pain through the spinal cord may be inhibited by vitamin D's suppression of TNF-α and of the negative activities of astrocytes and microglia. Vitamin D also has a role in regulation of neurotransmitters within the brain, such as acetylcholine, dopamine, and serotonin.[97]

Animal data have suggested also that pain-sensing neurons produce and respond to active vitamin D metabolites via vitamin D receptors.[106] Despite the disparity of data related to supplementation from clinical trials, evidence is sufficient to support a potentially beneficial clinical effect for vitamin D in nonspecific musculoskeletal pain of unknown origin, particularly in patients with low vitamin D status.

Lipoic Acid. Lipoic acid (LA), also known as thioctic acid, can be synthesized by the body de novo from fatty acids and cysteine but only in very small amounts.[107] The primary source of LA comes from foods such as red meat and organ meats and from plant sources such as spinach, broccoli, tomatoes, brussels sprouts, and rice bran. LA is a compound with important antioxidant activity, mediated through its ability to induce glutathione synthesis; recycle key antioxidants, such as vitamin C, vitamin E, and coenzyme Q_{10}; and act as a metal chelator.

LA has been used for decades in Europe for the treatment of diabetic neuropathy. A large clinical trial using 600 mg/d of LA for 4 years (NATHAN trial) found significant improvements in several of the assessed parameters, including the overall neuropathy impairment score and muscular weakness; however, the primary outcome, a composite score, did not reach significance.[108] A meta-analysis of LA for peripheral neuropathy in people with diabetes found an overall reduction in total symptom scores of -2.26 ($P < .0001$), with the greatest effect seen with intravenous dosing versus oral administration (-2.81 vs -1.78).[109]

In another recent human study in diabetic neuropathy, low-dose oral LA (200 mg/d) was compared with the available pharmaceutical treatments, carbamazepine and pregabalin, for a 6-month intervention period. LA was stated to be therapeutically equivalent to pregabalin, although the latter had a quicker onset of action and better results, and carbamazepine was inferior to both.[110]

Possible mechanisms of action of LA, at least in experimental diabetic neuropathy, include a reduction of oxidative stress and improvements in nerve blood flow and nerve-conduction velocity (NCV). More important, LA has been shown to benefit factors such as glucose utilization and glycation, both of which may have important upstream benefits in diabetic neuropathy.[111]

Further insights into the possible mode of action of LA come from a rodent model of neuropathic pain in multiple sclerosis, where subcutaneous administration of R-lipoic acid was found to be very effective at reducing pain sensitivity. The mechanism of action was thought to be a reduction of augmented cluster of differentiation 3 (+) t-cell infiltration and a reduction in signaling of brain-derived neurotrophic factor (BDNF)-tropomyosin receptor kinase B-extracellular signal-regulated kinases in the spinal dorsal horn. BDNF is found in terminals of nociceptive primary afferents and has a positive effect on glutamate transmission in the spinal cord.[112]

The specific antioxidant and anti-inflammatory properties of LA seem to be particularly useful in nerve injury. Significant neurorestorative effects have been seen in animal models,[113] which explains the positive effects of LA in neuropathic pain conditions.

Vitamin C. A number of meta-analyses and systematic reviews concerning complex regional pain syndrome (CRPS) and vitamin C have been published in recent years. Most,[114-116] but not all,[117] have concluded that vitamin C may be useful in the treatment of CRPS or in the prevention of surgically induced CRPS. Although all of the reviews included upper-limb fractures, one paper concluded that vitamin C could be of use in the lower limbs as well.[116]

The most recent review concluded that a moderate level of evidence supported the adjunctive preoperative use of 2 g of vitamin C to reduce postoperative morphine consumption.[114] The same review also found a high level of evidence supporting 1 g per day of perioperative vitamin C supplementation for 50 days for prevention of postsurgical CRPS type 1.

The clinical practice guidelines of the American Academy of Orthopedic Surgeons on the treatment of distal radius fractures states moderate evidence exists for adjuvant treatment with vitamin C for the prevention of disproportionate pain.[118] Together, these studies support the use of vitamin C both as a preventive tool and as a means of supporting recovery postinjury and postsurgery.

Therapies Involving Meditation. Increases in experienced pain have been clearly associated with increased brain activity in a set of regions involved in affective and cognitive modulation of pain, including the anterior cingulate cortex, anterior insula and sensory areas, and thalamus and posterior insula.[119] The prefrontal cortex (PFC) is thought to underlie evaluation, appraisal, or memory related to painful stimuli.[120] Brain imaging studies have found that each form of meditation affects different combinations of these areas and, as such, the most efficacious form of meditation may vary between patients and/or conditions.[121] In this section, the current authors provide an overview of the known effects of the 3 best-supported forms of therapy involving meditation.

Mindfulness Meditation. Mindfulness meditation involves paying attention to what is happening in the moment rather than avoiding or withdrawing from those feelings. It has been found to reduce connectivity between brain regions involved in pain processing, particularly those involved in emotion, memory, and appraisal—the frontal cortices, amygdala, caudate, and hippocampus.

The reduction in those areas has also been associated with reduced sensitivity to pain.[119] Studies of the use of mindfulness for treating chronic pain have shown that changing the way patients relate to their pain can change their experience of pain, therefore decreasing the pain burden[122,123] and creating improved pain acceptance.[124]

Research on mindfulness and analgesia in clinical trials has produced mixed results, with confounding factors including different techniques and expertise being influential in effectiveness. Research has found mixed effects for mindfulness in the treatment of conditions such as fibromyalgia[125] and for management of chronic pain.[126,127] The differences in meditative practices are thought to be strongly influential in that regard. For example, it has been found that focused attention strategies have been far less effective than open monitoring techniques in which the individual is receptive to all thoughts.[120]

Meditation. Meditation, as opposed to mindfulness, has been more thoroughly investigated in relation to chronic pain of different etiologies. Through experimental pain studies conducted on experienced meditators such as Zen practitioners, much more is now understood about the different areas of brain activation, or reduced activation, in both the meditative and the nonmeditative state of experienced practitioners.

It has been shown that the experience of meditation can alter brain structures so that less pain is experienced on stimulus even when an individual is not in a meditative state. One study found that more experienced meditators perceived pain as less unpleasant than did controls, with meditation experience correlating inversely with unpleasantness ratings.[128] Meditation experts have been characterized by decreased activation in the dorsolateral and ventrolateral PFC regions and by enhancements in primary pain processing regions—the insula, somatosensory cortex, and thalamus.[129]

It should be noted that even where different meditation strategies did not have a significant positive effect on pain reduction, they did have a positive effect on mental health, which is likely to encourage the individuals to remain more optimistic about different pain management techniques.[130]

Yoga. Yoga, deriving from ancient Indian philosophy, combines exercise, stretching, relaxation, breathing techniques, and meditation. Evidence suggests that yoga is moderately effective for the management of pain and functional outcomes across a range of musculoskeletal conditions.[131] It has also been found to have positive effects on brain waves for many clinical neurological conditions, such as anxiety and depression,[132] that have a strong relationship to increased sensitization of pain processing.

A recent meta-analysis on yoga for low-back pain found strong evidence for both short- and long-term improvements in pain as well as significant decreases in back-specific disability.[133] The mechanisms of these improvements are likely to be 2-fold, incorporating the positive neuropsychological effects of meditation, with a physical release of tight muscles and increased flexibility, which may decrease pain production from affected areas. Yoga has also proven effective for other types of pain, including rheumatoid arthritis and headaches.[134] A systematic review of Iyengar yoga for treatment of spinal—back and neck—pain found strong evidence for short-term effectiveness but little evidence for long-term effectiveness of yoga in 6 clinical trials.[135]

Although the literature surrounding yoga for chronic pain is far from extensive, brain scans from an experienced yoga practitioner have shown clear signal changes in response to painful stimulation in 3 key areas of pain processing: the thalamus, the insula, and the cingulate cortex.[136] In addition, a cross-sectional study on American yoga practitioners found experienced asana-based yoga practitioners, with 6 to 11 years of experience, had increased grey matter, mostly in the insular cortex, a primary point for pain processing.[137] This increase in grey-matter volume was found to be correlated with increased pain thresholds exhibited during thermal and pain-threshold tasks.

Additional Therapeutic Options. Additional therapeutic options have been studied. Several systematic reviews have occurred on the benefits of acupuncture for chronic low-back pain and other chronic pain states,[138,139,140] showing significant reductions in pain.[141] The neural mechanisms underlying this analgesia are complex. The insertion of needles activates all types of afferent nerve fibers—Aβ, Aδ, and C—and can induce an analgesic effect. Diverse signal molecules, such as opioid peptides, glutamate (NMDA and AMPA/kainate [KA] receptors), and 5-HTP also contribute to mediating acupuncture analgesia. Among them, the opioid peptides and their receptors in the spinal dorsal horn are thought to play a pivotal role in mediating acupuncture analgesia.[142]

Similarly to acupuncture, transcutaneous electrical nerve stimulation (TENS) also works by activating opioid receptors, with low-frequency (LF) activating the μ-opioid receptors and high-frequency (HF) activating the δ-opioid

receptors.[143] Pharmaceutical opioid analgesics affect the μ-opioid receptors; therefore, in patients with developed opioid tolerance, LF may not be effective. However HF has been shown to be of benefit in that population.[144,145] TENS used on acupuncture points, known as acupuncture-like TENS, may increase the analgesic effect.[145] A Cochrane review for use of TENS in chronic pain found positive analgesic outcomes in favor of active TENS treatment, with the majority of studies finding no difference in analgesia between HF and LF.[146]

The application of ice packs (cryotherapy) is often used in acute pain management to reduce inflammation and swelling by slowing the cells' metabolic rate. Meta-analyses of postsurgical ice-pack applications have shown significant reductions in pain,[147,148] which have been shown in many randomized controlled trials to relate directly to reduction in narcotic use following surgery.[149-151] In addition to its usefulness in acute pain, cryotherapy is thought to decrease the negative neuroplastic changes that can lead to chronic pain. The proposed mechanism of the therapy is a reduction in free-nerve-ending sensitivity, which increases nerve firing thresholds and decreases NCV. Cold-water immersion was able to reduce sensory NCV by 22.6 m/s and motor NCV by 8.3 m/s in clinical testing,[152] thus increasing participants' pain thresholds.

DISCUSSION

Chronic pain is a major health issue, affecting more patients than any other chronic disease. Directly or indirectly, chronic pain affects sleep, mood, energy levels, and many other aspects of patients' well-being and quality of life. Unfortunately, the way practitioners traditionally treat pain in general is unsatisfactory.[8] The aims of the current article were to review the evidence-based complementary therapies for treatment of chronic pain and to begin discussions regarding how those therapies could fit into an individualized, multimodal approach aimed at decreasing the prevalence of chronic pain.

Chronic pain results in complex, adaptive changes—neuroplasticity—in all 3 orders of neurons, and those changes ultimately increase the transmission and/or perception of pain. Interestingly, a number of studies have found that these changes can be reversed with successful therapy.[153] The spiral-like effect of these changes has led the current authors to the hypothesis that treating multiple targets could address the pain more effectively,[9,154] whereas simultaneously reversing the neuroplastic changes more quickly. The authors believe that this method needs to be investigated.

The available evidence suggests that efficacious complementary therapies exist that target all 3 orders of neurons. For instance, in the first order of neurons, capsaicin blocks TRPV1-positive nociceptors and decreases the density of epidermal nerve fibers. Curcumin exerts an anti-inflammatory effect in the extremities and possibly in the spinal cord through the reduction of prostaglandins, TNF-α, interleukins, and NO. Yoga and meditation have been shown to change white and grey matter within important pain-processing and pain-modulation centers in the brain. Vitamin D and omega-3 fatty acids appear to have potential roles in normalizing all 3 orders of neurons.

However, given the fact that only a small subset of any cohort is likely to respond to any given therapy, approaches other than suggesting the same combination for all patients with the same disorder should be investigated.[8] One approach that is likely to be used in the future is to determine respondents to given therapies through their genetic and epigenetic coding and to target a number of specific areas along the pain pathway using therapies that are efficacious for that individual.[155,156] Unfortunately, until such pharmacogenetic strategies are available, the process of determining responses to individual therapies or combinations of therapies is likely to be a long and laborious process for the clinician.

Pharmaceutical therapy plays a pivotal role in the treatment of chronic pain, and the current authors are by no means suggesting its elimination. Despite the fact that the best pharmacological intervention for chronic noncancer pain yields about 30% reduction in about half the patients treated,[4] a given pharmaceutical may remain the most efficacious individual therapy in a multimodal individualized approach. However, for medicines such as opioids, NMDA-receptor antagonists, and anticonvulsants, many patients cannot continue their medication due to the short- or long-term side effects experienced.

It is likely that a multimodal therapy, including efficacious complementary therapy, will decrease the need for or amount of such medications.[9,154] In any event, frequent assessment of the costs and benefits of every therapy should be made. Monetary costs are also important to consider, and as such, complementary or conventional therapies that have few adverse effects but achieve little benefit for the individual patient should be withdrawn.

CONCLUSIONS

A number of complementary therapies may be efficacious in reducing chronic pain and/or the need for analgesics that have a less favorable adverse effect profile. These therapies include curcumin, capsaicin, vitamin D, omega-3 fatty acids, LA, acupuncture, yoga, meditation, mindfulness meditation, and others. It is important to consider, however, that none of these therapies will be effective for all patients.

Given that chronic pain results in complex adaptive changes that occur along the pain pathway and that these changes are likely to be different in different patients, the current authors have suggested a model of chronic pain treatment involving multimodal, individualized treatment, targeting multiple sites along the pain pathway. Unfortunately, until practitioners can use pharmacogenetics to predict responders to any particular therapy or groups of therapies, an individualized, multimodal, chronic pain treatment will continue to be a process of trial and error.

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